Dear Editorial Office,

We thank you and the reviewers for your excellent and thoughtful review of the manuscript. Below we have detailed changes made to the manuscript in response to the reviewer and your comments.

EDITORIAL OFFICE COMMENTS

Science Editor:

Issues raised:

1. PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

2. The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text

Response to Editor’s Comments:

We thank the editorial office for their prudent comments. We have fixed reference formatting as advised. However, we believe the “Article Highlights” is only used for scientific research articles (judging by the review/minireview format and guidelines pdf on your website and minireviews/reviews published in the last three issues)? Therefore, we have not included an Article Highlights.

REVIEWER COMMENTS

Reviewer 1:

This paper was well written. The authors discussed the most current classifications of panNENs based on pathology, genetics, clinical features, and imaging techniques. In my view, malignant tumors are heterogeneous with internal spatial variations secondary to diferences in angiogenesis and cellularity, and tumors with aggressive behavior and poor prognosis have higher intratumoral heterogeneity. Notably, texture analysis is a potentially useful tool that evaluates tissue gray-level intensity and pixel position within an image and allows quantifcation of tumor spatial heterogeneity. Texture analysis or radiomics based on CT/MRI or PET/CT has been investigated in staging of PNETs or prognosis prediction.

Response to Reviewer 1:

We thank the reviewer for highlighting this. Discussions of texture analysis and its use to grade/differentiate panNEN, as well as predict outcomes, has been added to the manuscript as follows:

"The potential use of CT, MRI, and positron emission tomography/computed tomography (PET/CT) texture analysis to grade tumors and predict clinical outcome will also be briefly highlighted."

"CT radiomics may be useful for distinguishing the grade of panNEN based on tumor heterogeneity and spatial variation when imaging findings are ambiguous. Texture analysis interprets the distribution of pixel values and position within an image to provide objective, quantitative evaluation of tissue heterogeneity. Guo et al found texture parameters such as mean grey-level intensity, entropy, and uniformity demonstrated adequate sensitivity (73-91%) and specificity (85-100%) when differentiating grade 1 and 2 panNET from grade 3 panNEC, suggesting texture analysis may be useful for staging panNEN. Mean grey-level intensity showed up to a 100% sensitivity and 91% specificity for distinguishing grade 1 and grade 2 panNET[22]. Canellas and colleagues reported significant differences between low-grade (grade 1) and high-grade (grade 2 and 3) panNEN in texture parameters including skewness, mean of positive pixels, and entropy. However, the only parameter that was an independent predictor of tumor grade was entropy. In addition, further investigation and standardization of postprocessing techniques is required before texture analysis can be applied in a clinical setting[23]."

"Histogram analysis of ADC maps could be useful for further indicating the aggressiveness and spread of panNEN. ADC entropy and kurotsis were reported to increase with tumor grade and vascular invasion. These parameters may also be useful

for distinguishing panNEN with lymph node or distant metastasis, as both increase with the presence of metastases[31].”

“The use of SSA-PET/CT combined with texture analysis may also be a useful indicator of prognosis. A multi-center retrospective study demonstrated higher entropy could predict greater overall survival[37].”

“CT texture analysis may be useful as panNEC are typically demonstrate more intratumoral homogeneity than PDAC. Consequently, panNEC demonstrate higher uniformity and lower entropy than PDAC at portal phase imaging[50]. Texture analysis based on ADC values may also improve diagnostic capabilities; ADC histogram analysis of diffusion-weighted imaging revealed PDAC demonstrate higher kurtosis and skewness on ADC_{400} and ADC_{800} than panNEN, overall. PanNEN exhibited significantly lower entropy regardless of b value[31].”

“Other methods for predicting PRRT response include the measurement of skewness and kurtosis based off 68Ga-DOTATATE imaging; Önner et al reported significantly higher skewness and kurtosis in tumors which did not response to treatment that those that did. Nevertheless, the diagnostic ability of the two metrics to indicate poor PRRT response remained moderate to low[73].”